

[CASE REPORT]

Peribronchial Connective Tissue Infection Caused by *Bifidobacterium longum* and *Veillonella* Species Mimicking Lung Cancer

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Abstract:

An 86-year-old woman was admitted for the investigation of atelectasis of the upper lobe of her right lung with a mass shadow in the hilum (Golden S sign). Chest computed tomography revealed swollen connective tissue around the right bronchus, and needle aspirate grew *Bifidobacterium longum* and *Veillonella* species. She was diagnosed with peribronchial connective tissue infection, and her condition improved with antibiotics. Although this sign is strongly suggestive of malignant disease, benign disease should be considered in the differential diagnosis. Pulmonary infection caused by *Bifidobacterium longum* is extremely rare; however, clinicians should consider it as a possible cause of pulmonary infections.

Key words: peribronchial connective tissue infection, *Bifidobacterium longum*, *Veillonella*, Golden S sign

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Introduction

Atelectasis of the right upper lobe of the lung with mass shadow in the right hilum on chest radiograph is known as the Golden S sign (inverted S sign), and typically associated with right upper lobe atelectasis due to lung cancer (1-4).

Bifidobacteriaceae are non-motile obligate anaerobic Gram-positive rods, found among mouth commensals and flora of the gastrointestinal and female genital tracts. Although *Bifidobacteriaceae* have long been considered non-pathogenic and advocated as a probiotic, they occasionally cause opportunistic infections (5-7).

We herein report a case of peribronchial connective tissue infection caused by *Bifidobacterium longum* (*B. longum*) and *Veillonella* species in an immunocompetent patient with positive Golden S sign who was suspected of having lung cancer.

Case Report

An 86-year-old woman visited her primary care doctor

with wheeze and general malaise as her chief complaints. Chest radiography revealed atelectasis of the upper lobe of her lung with a mass shadow in the right hilum (the Golden S sign). These findings suggested a diagnosis of lung cancer, and she was admitted to our hospital for a further investigation.

She had a history of hypertension and hyperlipidemia, and was receiving telmisartan 40 mg, amlodipine 5 mg, pitavastatin 1 mg. She was a non-smoker with no history of alcohol abuse or using probiotics containing *Bifidobacteriaceae*.

A physical examination revealed a body temperature of 38.4°C, blood pressure of 120/85 mmHg, heart rate of 92 beats per minute, respiratory rate of 30 breaths per minute, and percutaneous oxygen saturation of 91% while breathing room air. Her heart sounds were normal, but an expiratory wheeze was audible over the right middle lung field. Other systemic examinations were normal.

Blood tests revealed the following: white blood cell count, 5,590/ μ L (Neutrophil: 78.2%); red blood cell count, 442 \times 10³/ μ L; hemoglobin level, 13.2 g/dL; hematocrit, 38.3%; platelet count, 17.8 \times 10⁴/ μ L; and C-reactive protein, 20.5 mg/

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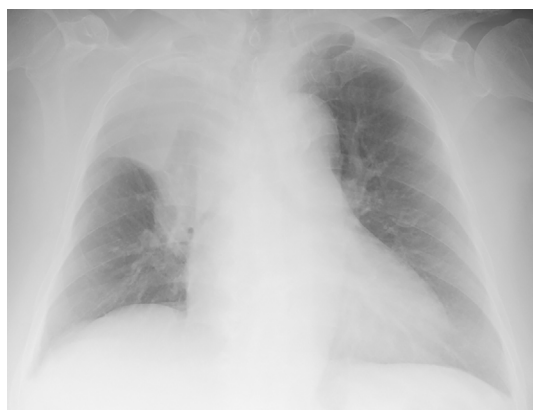


Figure 1. A chest radiograph showing collapse of the upper lobe of the right lung over a reverse S-shaped minor fissure (Golden S sign).

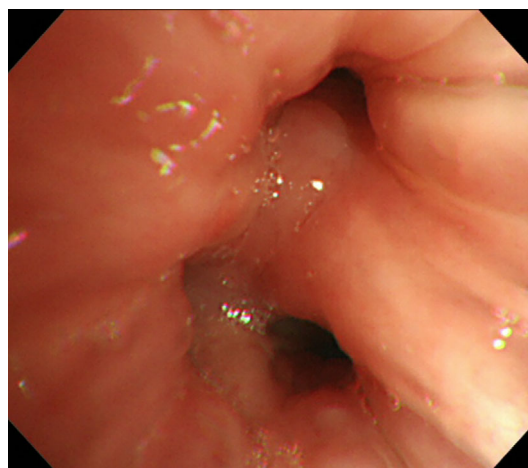


Figure 2. Bronchoscopy on day 5 showing edematous mucous membrane in the right upper lobe bronchus.

dL. Other tests revealed mild liver dysfunction and a normal renal function. Her serum carcinoembryonic antigen, cytokeratin subunit 19 fragment, and pro-gastrin-releasing peptide levels were within the respective normal ranges.

Chest radiography (Fig. 1) showed right upper lobe atelectasis and elevation of the minor fissure with a mass located in the right hilum (Golden S sign). Chest computed tomography (CT) showed atelectasis of the right upper lobe of her lung, abrupt cutting of the right upper lobe bronchus and swollen tissues around the right bronchus.

Although bronchoscopy on day 5 revealed edematous mucous membrane in the right bronchus, the orifice of the right upper lobe bronchus was not obstructed (Fig. 2). Transbronchial needle aspirate obtained through the right upper lobe bronchial wall showed no malignant cells; however, cultures of the pus were positive for anaerobic Gram-positive bacilli and Gram-negative cocci. Culture for mycobacteria was negative. The cultured bacteria were subjected to a 16S ribosomal RNA gene sequence analysis in the Miroku Medical Laboratory (Nagano, Japan). The result of the 16S ribosomal RNA gene sequence isolated anaerobic Gram-positive bacilli that showed 99.7% identity with that of *B. longum* type strain Su 851 (GenBank accession number AB924532) and anaerobic Gram-negative cocci that showed 99.3% identity with that of *Veillonella parvula* type strain (CP001820) and 98.9% identity with that of *Veillonella tobetsuensis* type strain (NR_113570). According to these findings, the patient was diagnosed with peribronchial connective tissue infection caused by *B. longum* (MML4440: DDBJ accession number LC565384) and *Veillonella* species (MML4439: DDBJ accession number LC565383).

She received 3 g of ampicillin sodium/sulbactam sodium intravenously 4 times daily. Chest radiography carried out the next day showed that the right upper lobe of her lung had re-expanded. Chest contrast-enhanced CT on day 7 (Fig. 3) showed irregularly enhanced swollen connective tissues around the right bronchus. Antibiotic treatment was changed to oral amoxicillin/clavulanate potassium on day 23, and she was treated for 28 days. The treatment led to a

gradual improvement in her symptoms and laboratory findings. Chest contrast CT on day 73 (Fig. 4) revealed that the swollen connective tissue around the right bronchus had disappeared.

Discussion

This case report highlights two important points. First, the Golden S sign was observed in a patient with non-malignant disease. Second, although infections caused by *Bifidobacteriaceae* are extremely rare, such a pulmonary infection developed in an immunocompetent woman.

The Golden S sign is seen on chest radiography when the right upper lobe of the lung collapses due to a centrally located mass. The minor fissure is concave peripherally but convex centrally, causing the shape of the fissure to resemble an S, hence the name. This sign is highly suggestive of a neoplasm, such as primary lung cancer, but other malignant conditions, such as metastatic lung cancer, malignant lymphoma, mediastinal tumor, or enlarged lymph nodes, may also produce this sign (1-4).

In the present case, *B. longum* and *Veillonella* species were cultured from the transbronchial needle aspirate, and the patient was diagnosed with peribronchial connective tissue infection. Therefore, this anaerobic infection produced the Golden S sign. Cases of benign diseases presenting with a Golden S sign are rare. Although the Golden S sign has been reported in patients with pulmonary fungal infection and patients with lymph node enlargement due to tuberculosis (1, 2), this is the first report of a Golden S sign being caused by *Bifidobacterium longum* and *Veillonella* species.

Although the Golden S sign should serve to alert the clinicians to the high possibility of malignant disease (3, 4), benign diseases should be considered in the differential diagnosis of patients with the Golden S sign.

Although *Bifidobacterium* species consists of more than 50 species, only 10 species are found in humans, and *B. longum* is the representative organism. Some *Bifidobacte-*



Figure 3. A, B: Chest contrast-enhanced CT on day 7 showing enhanced swollen connective tissues around the right bronchus.

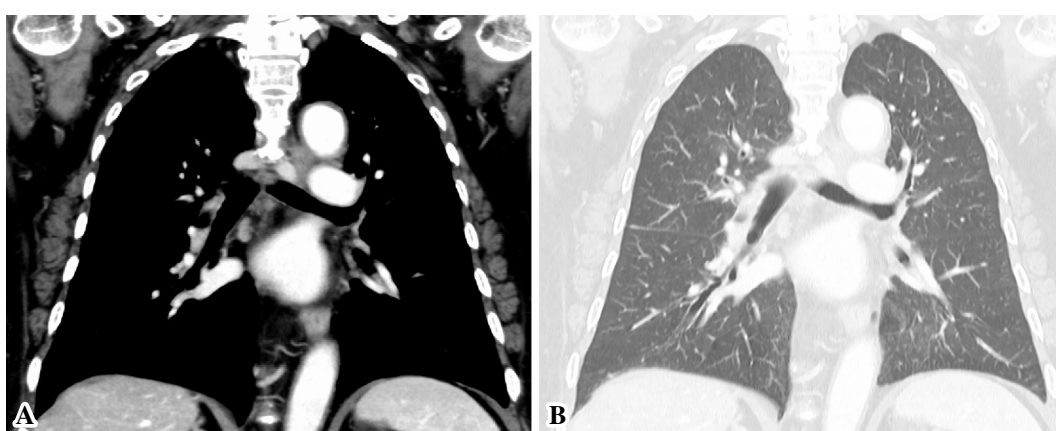


Figure 4. A, B: Chest contrast-enhanced CT on day 73 showing that the swollen connective tissue around the right bronchus had disappeared.

Table. Characteristics of Patients with *Bifidobacterium* Pulmonary Infections.

Age/ Sex	Underlying disease	Diagnosis	Isolated organism	Treatment	Outcome	Reference
33/M	-	Pneumonia	<i>Bifidobacterium dentium</i>	penicillin, ampicillin	Improved	[20]
52/M	Alcoholism	Necrotizing pneumonia	<i>Bifidobacterium dentium</i>	penicillin G, kanamycin, gentamicin	Dead	[21]
47/M	Tuberculosis Diabetes mellitus	Lung abscess, Empyema Empyema	<i>Bifidobacterium</i> sp.	clindamycin, cefozopran	Improved	[22]
67/M	Lung cancer	Lung abscess	<i>Bifidobacterium</i> sp.	not reported	Improved	[13]
86/F	-	Peribronchial connective tissue infection	<i>Bifidobacterium longum</i>	ampicillin/sulbactam, amoxicillin/clavulanate	Improved	Present case

rium species are used as probiotics to promote health of the gastrointestinal tract (5-8). *Bifidobacterium* species other than *Bifidobacterium dentium*, which causes dental caries and related diseases, rarely cause invasive human infections (9). Several cases of human infections caused by *Bifidobacterium* species, such as bacteremia (5, 6, 8, 10), meningitis (11), peritonsillar abscess (12), pulmonary infection (6, 13), peritonitis (7), necrotizing pancreatitis (14, 15), epidural abscess (6), urinary tract infection (16-18), and

shunt infection (19) have been reported. Most previous reports of *Bifidobacteriaceae* infections have been opportunistic infections in immunocompromised patients (7); however, our patient was not immunocompromised. A literature search revealed only four case reports of patients with *Bifidobacterium* pulmonary infections (Table) (13, 20-22).

Veillonella species, an anaerobic Gram-negative coccus, is part of the normal flora of the oral cavity, upper respiratory tract, gastrointestinal tract, and female genital tract. There

have been case reports of meningitis, pulmonary infections (23), head and neck infections, skin and soft tissue infections, and peritonitis caused by this organism. *Veillonella* species are usually recovered together with other organisms as co-infections. In this case, *Veillonella* species were isolated with *B. longum*. Although little is known about the virulence and clinical significance of *B. longum*, we suspect that these two organisms caused polymicrobial infection in our patient. However, the route of infection is unknown. There were no findings suggesting laryngitis or mediastinitis, so we speculate that the route was through the respiratory tract by aspiration.

Tena et al. (7) suggested that infections caused by *Bifidobacteriaceae* may be overlooked or underreported, since this family of bacteria is considered part of the normal microbiota. In addition, these organisms may not be recovered, as they are difficult to identify due to their fastidious growth requirements and the difficulty in distinguishing the organisms from other Gram-positive anaerobic bacilli using conventional tests.

In conclusion, although the Golden S sign is strongly suggestive of malignant disease, benign disease should be considered in the differential diagnosis of patients with this sign. Although pulmonary infections caused by *Bifidobacterium* species are extremely rare, especially in immunocompetent individuals, clinicians should be aware that this organism can cause pulmonary infections, and should provide appropriate treatment if this organism is identified.

The authors state that they have no Conflict of Interest (COI).

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